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REVIEW ARTICLE

Heat Shock Protein 60 in Vascular Biology

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Abstract

The response of heat shock proteins (HSPs) to stress-induced stimuli is now well documented and understood. Specific HSPs like HSP70 play an important role in vascular diseases like atherosclerosis and hypertension. However, the involvement of other HSPs in these vascular pathologies has been largely ignored. HSP60 plays a particularly critical role in vascular cell growth, an important component of many vascular pathologies. HSP60 directly induces vascular smooth muscle cell proliferation. The mechanism may involve an HSP60-induced stimulation of the rate of nuclear protein import in the smooth muscle cell. HSP60 expression levels also correlate with the severity of the disease. In conclusion, HSP60 may have an important role to play in vascular diseases like atherosclerosis. HSP60 may be a promising future pharmaceutical target to focus upon in order to deter the pathological effects of disease conditions like hypertension and atherosclerosis.

Key words: Heat shock proteins; Atherosclerosis; Nuclear proteins; Nuclear protein import; Hypertension.

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Introduction

A cellular stress response is a reaction to any form of damage that pushes the cell out of its homeostatic set point.[1] When exposed to environmental stressors, cells can mount an adaptive response to promote survival or in the face of more severe damage initiate controlled cell death.[2] Some of the protective mechanisms include the heat shock response, unfolded protein response, DNA damage response and oxidative stress response.[2] Proteins in these stress-response pathways are conserved across human, yeast, bacterial and archaeal genomes, underscoring their importance in protecting cells from environmental stressors.[1] Impairment in the function of these pathways may contribute to many pathologies, such as atherosclerosis.

Heat shock response

The heat shock response is defined as the activation of a subset of genes which were previously inactive or expressed at low levels, in response to mild hyperthermia or other stresses.[3] This phenomenon was first described in 1962, when Ritossa discovered a unique puffing pattern on the chromosomes of salivary gland cells in *Drosophila* subjected to an elevated temperature.[4] Puffs are chromosomal sites of rapid RNA synthesis and thus represent regions of gene activation.[5, 6] The puffs induced by heat shock treatment were associated with the expression of a new family of proteins, now called heat shock proteins (HSPs).[5] In addition to elevated temperature, other stressors including oxidative stress, heavy metals, bacterial and viral infections turn on the heat shock

response and induce the expression of HSPs.[7, 8] HSPs are involved in both cardiac and vascular diseases (Table 1).

Table 1: Heat shock proteins (HSPs) involvement in atrial fibrillation and atherosclerosis

Heat shock protein	Cardiovascular disease	Involvement
HSP27	Atrial fibrillation	Protective
HSP60	Atrial fibrillation	Protective
	Atherosclerosis	Promotes
HSP70	Atrial fibrillation	Protective
	Atherosclerosis	Promotes
HSP90	Atrial fibrillation	Protective
	Atherosclerosis	Promotes

Heat shock proteins

HSPs are a family of evolutionarily conserved chaperone proteins that are induced in response to a variety of stress stimuli to attenuate cellular damage and promote survival.[9] These chaperones protect cells in the face of proteotoxic stress by facilitating proper folding or refolding of proteins to prevent protein aggregation.[10] Beyond their role in the stress response, HSPs have several roles in maintaining cellular homeostasis including, regulation of protein breakdown,[11, 12] cell signalling pathways[13, 14] and intracellular protein trafficking,[15, 16] as well as regulation of apoptotic pathways.[7, 9, 17] HSPs are named according to their molecular weight and are divided into the following sub-families based on their amino acid constitution and function: HSP110, HSP90, HSP70 and HSP40; small HSPs and human chaperonins (HSP60/HSP10, TRiC).[18]

The HSP70 and HSP90 families have critical roles in cellular proteostasis and exhibit similar structural properties.[10, 19] In humans, some HSP70 and HSP90 family members are constitutively expressed, while other members have low basal expression and are induced under stress conditions.[10, 18, 20] These chaperones primarily function in the cytosol and the nucleus, but both families also have isoforms that localise to the mitochondria and endoplasmic reticulum.[10, 19, 21, 22] HSP70 functions include facilitating the folding of newly synthesised polypeptide chains, re-folding of misfolded proteins to prevent their aggregation, movement of proteins across intracellular membranes and control of proteins involved in cell signalling and apoptosis.[10, 15] HSP90 mediates the folding, activation, transport and degradation of proteins involved in cell cycle regulation, cellular signalling and apoptosis.[19]

HSP70 and 90 share similar structural motifs, both possessing an ATP-binding domain as well as binding domains for client proteins and regulatory co-chaperones.[23] The chaperone activity of these proteins is ATP dependent such that ATP and ADP-bound forms assume different conformations to enable the binding of different substrates.[24-26] Thus, the configuration and corresponding function of both protein families is dependent on their ATPase activity, which can be modulated by co-chaperones (eg HSP70-HSP40; HSP70/HSP90 organising protein, Hop; HSP110-HSP70)[19, 26] and post-translational modifications (ie phosphorylation and acetylation).[23] For example, HSP110 in complex with HSP-70 acts as a nucleotide exchanger for ADP-bound HSP70 to cooperatively facilitate disassembly of protein aggregates.[27, 28]

The small HSPs (sHSPs) are lower molecular weight (12-42 kDa) chaperones with a conserved α-crystallin domain.[29] At baseline, most proteins in this sub-family have low levels of expression.[2, 29] sHSPs interact with a range of client proteins, particularly those involved in gene expression, signal transduction, apoptosis and cytoskeletal organisation.[30, 31] HSP27 is a seminal family member which is induced as part of the heat shock response in most tissues.[32, 33] HSP27, like HSP70 and HSP90, is a pro-survival chaperone.[29, 34] Induction of HSP27 has been shown to protect cells against stress-induced apoptosis.[34-36] In addition, HSP27 interacts with actin to maintain cytoskeletal integrity and promote survival in the face of stress stimuli.[2, 30]

sHSPs are ATP-independent chaperones which form dynamic oligomeric structures around unfolded proteins to hold these client proteins in a partially competent state[37] until transfer to ATP dependent chaperone complexes like HSP70/40 to refold the protein.[38-40] Alternatively, sHSPs can transfer unfolded proteins to proteasomes for degradation.[11, 12] The chaperone activity of sHSPs is regulated by phosphorylation,[40] temperature[41] and pH.[42]

The chaperonin family includes HSP60, the eukaryotic homolog of GroEL and its co-chaperone

HSP10 (eukaryotic homolog of GroES) as well as the TRiC protein family.[18] HSP60 has an intracellular role as a housekeeping and stress-induced protein chaperone that aids in the folding and maintenance of a diverse set of client proteins.[43-45] HSP60 exhibits its chaperone activity through the assembly of 2 groups of HSP60 monomers into a barrel-like structure containing a central core which binds unfolded proteins.[46-49] Protein unfolding and re-folding within this multimeric HSP60 structure is ATP dependent and assisted by its co-chaperone, HSP10.[49, 50] HSP60 also functions to prevent protein aggregation within the mitochondria.[51]

Within the cell, the majority (80-85 %) of HSP60 is localised to the mitochondria, with a smaller fraction (15-20 %) localised to the cytosol and plasma membrane.[52, 53] In response to stress, mitochondrial HSP60 redistributes into the cytosol[54] and can be released from cells in vesicles.[43] Extracellular HSP60 functions as a signaling molecule, promoting an inflammatory response through toll-like receptor (TLR) activation of various cell types.[55] For example, direct exposure of cultured vascular smooth muscle cells (VSMCs) to recombinant HSP60 promotes pro-inflammatory cytokine release, migration and proliferation.[56, 57] Alternatively, intracellular increases in HSP60 expression in response to stress can promote apoptosis or proliferation depending on the cell type.[45, 54, 58-60] For example, artificial increases in intracellular HSP60 protein levels through adenoviral transfection can directly stimulate VSMC proliferation.[58, 59]

Heat shock protein 60 and atherosclerosis

The association of HSP60 with heart disease has been recognised previously. For example, HSP60 is closely related with the development of atrial fibrillation.[51] The involvement of HSP60 with atherosclerotic vascular disease is worthy of research attention as well. The pro-inflammatory environment within atherosclerotic plaques effectively induces HSPs in vascular cells.[61] It is not surprising, then, that HSPs have been implicated in atherosclerotic development, with certain HSPs (HSP27 and HSP70) playing protective roles, while others (HSP90 and HSP60) are pro-atherogenic.[61-66] However, experimental atherosclerotic models and clinical studies have implicated HSP60 as the only HSP with the potential to directly contribute to atherosclerotic development.[62] HSP60 plays an important role in atherosclerosis in its role as an intracellular chaperone, intercellular signalling molecule and cell surface autoantigen.

Intracellular mechanisms of HSP60

Oxidised low-density lipoprotein (oxLDL) possesses a well-recognised capacity to induce atherosclerosis in both *in vitro* and *in vivo* conditions.[67] As shown in Figure 1, exposure of VSMCs to oxLDL in cell culture conditions induces cell proliferation, a process involved in atherogenesis.[58, 59] Native low-density lipoprotein (naLDL) does not possess this same capacity (Figures 2 and 3). Simultaneously, HSP60 expression is induced by the oxLDL, not naLDL, in a time and concentration dependent manner (Figures 2 and 3). Although this does not prove HSP60 is directly involved in atherogenesis, the indirect association of VSMC proliferation with HSP60 expression supports its involvement. More direct evidence is provided by overexpression of HSP60 in VSMC and the resultant induction of VSMC proliferation.[45]

Within surgically excised human atherosclerotic plaques, ECs, VSMCs and macrophages all display positive HSP60 staining.[68] In that same study, advanced lesions showed increased HSP60 expression in VSMCs and lymphocytes.[68] ECs subjected to shear stress *in vitro* and *in vivo* demonstrate increased HSP60 expression.[69] Furthermore, ECs from the aortic sinus in apoE deficient mice had high intracellular levels of HSP60 early in the development of atherosclerosis.[70] As atherogenesis proceeded, HSP60 was strongly expressed in the SMC-rich necrotic core.[70] In advanced, calcified plaques HSP60 expression was not detectable.[70] These studies suggest that intracellular HSP60 has an important role within different vascular cells throughout atherosclerosis. In particular, intracellular HSP60 has been suggested to promote VSMC proliferation under atherosclerotic conditions.[61] VSMCs infected with *Chlamydia pneumoniae*, an atherogenic stimulus, demonstrate increased cell proliferation, which coincides with

increased HSP60 expression.[46] Interestingly, in clinical studies, HSP60 expression was higher in *Chlamydia*-positive atherosclerotic plaques.[71] Furthermore, mechanical stretch and *Chlamydia pneumoniae* infection each have a synergistic effect on HSP60 expression and VSMC proliferation in oxLDL-treated cells.[58, 59] In addition, intracellular overexpression of HSP60 independently stimulates VSMC proliferation.[45, 58]

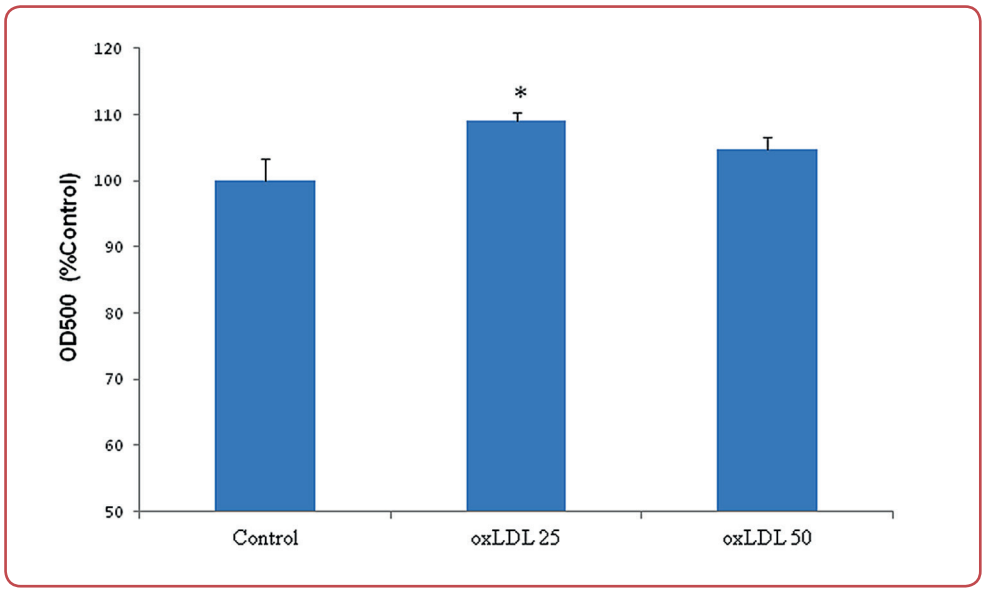

Figure 1: Oxidised low-density lipoprotein (OxLDL) stimulates vascular smooth muscle cell (VSMC) proliferation

*Rat VSMC proliferation in response to treatment with oxLDL at 25 or 50 µg/mL for 24 h. Control cells were incubated in identical medium without oxLDL. Cell number determined by optical density (OD) at 500 nm. Data represented as percentage optical density of control. *p < 0.05 versus control. Values are means ± SEM; n = 8.*

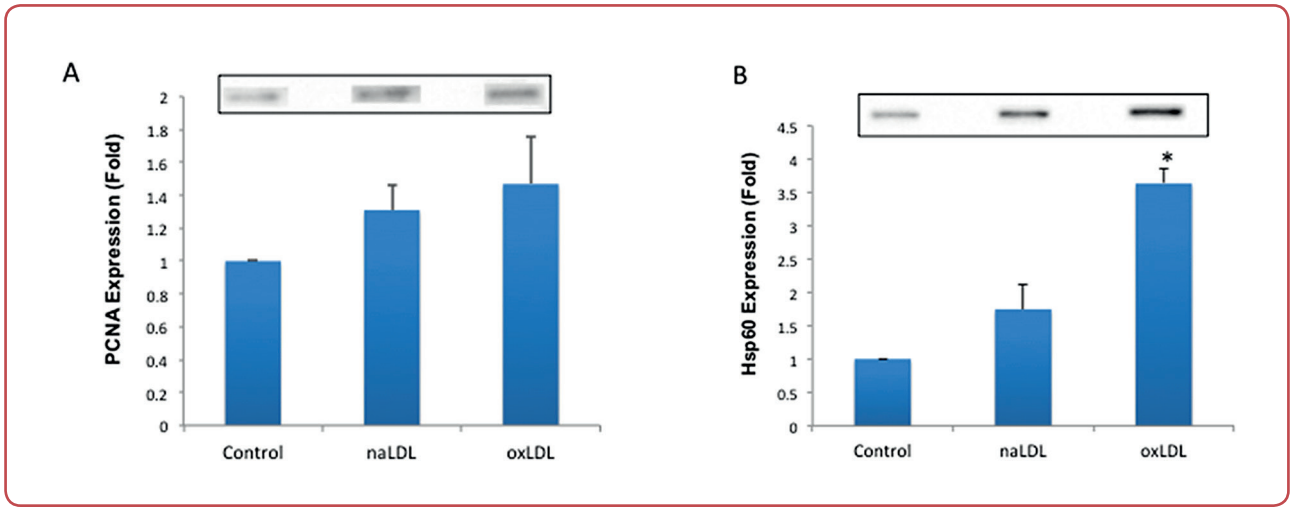

Figure 2: Effect of oxidised low-density lipoprotein (OxLDL) treatment on proliferating cell nuclear antigen (PCNA) and heat shock protein 60 (HSP60) expression in vascular smooth muscle cells (VSMCs)

*Western blot analysis and representative images of PCNA (A) and HSP60 (B) expression in rat VSMCs treated with native low-density lipoprotein (naLDL) or oxLDL at 25 µg/mL for 6 h. Control cells were incubated in identical medium without LDL. On each Western blot, density of a specific protein band was normalised by total protein loaded into each lane. Normalised protein expression is represented as fold change to control samples. The values in each graph represent the means ± SEM of three independent experimental repeats (n = 3) from the same primary rat aorta explant. *p < 0.05 versus control and naLDL.*

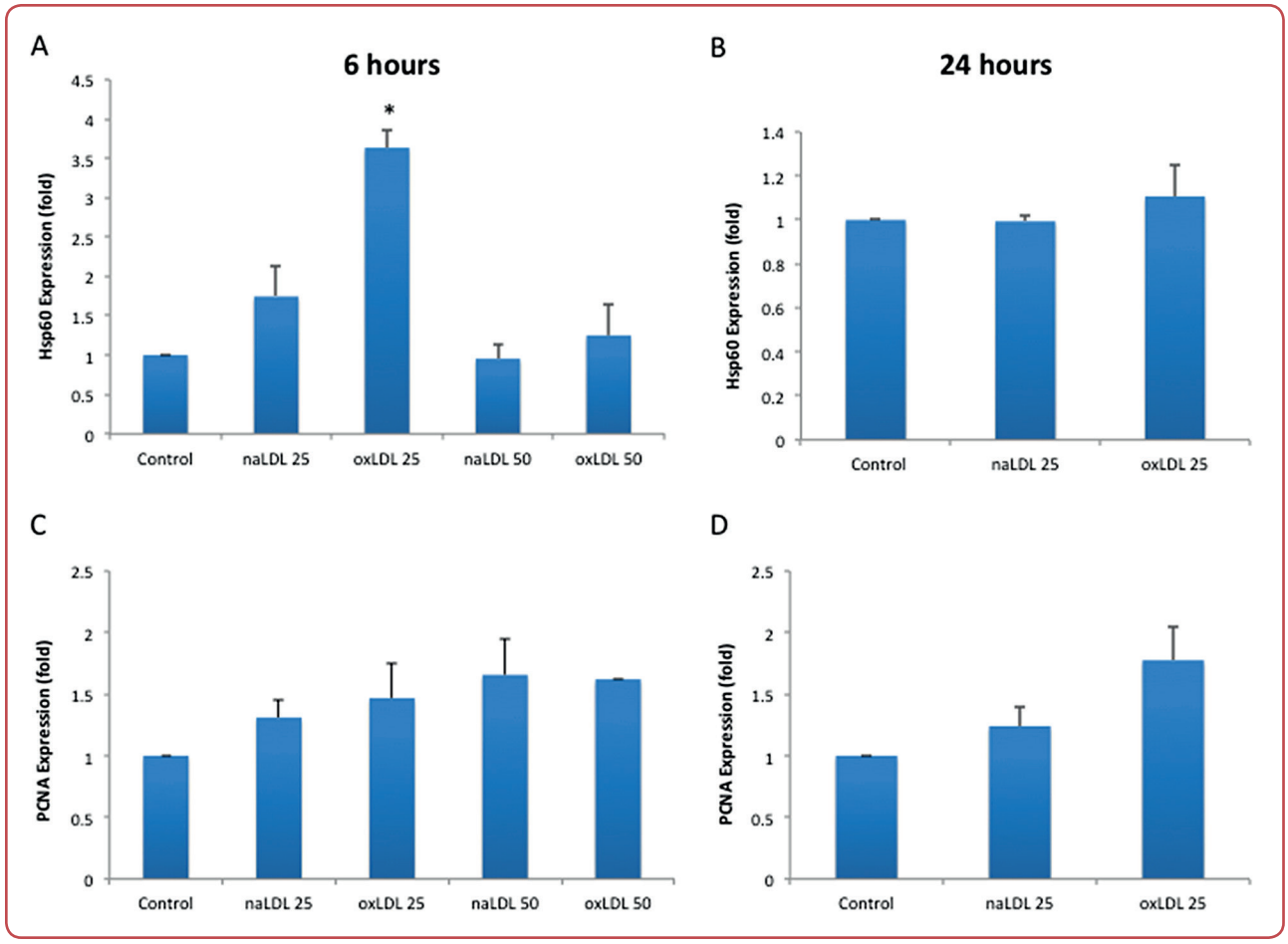

Figure 3: Effect of oxidised low-density lipoprotein (OxLDL) treatment for 6 or 24 hours on heat shock protein 60 (HSP60) and proliferating cell nuclear antigen (PCNA) protein expression in vascular smooth muscle cells (VSMCs)

*Western blot analysis of HSP60 (A, B) and PCNA (C, D) expression in rat VSMCs treated with native low-density lipoprotein (naLDL) or oxLDL at 25 or 50 µg/mL for 6 h (A, C) or 25 µg/mL for 24 h (B, D). Control cells were incubated in identical medium without LDL. On each Western blot, density of a specific protein band was normalised by total protein loaded into each lane. Normalised protein expression is represented as fold change to control samples. Values are means ± SEM; n = 3. *p < 0.05 versus 6 h control and naLDL at 25 µg/mL for 6 h.*

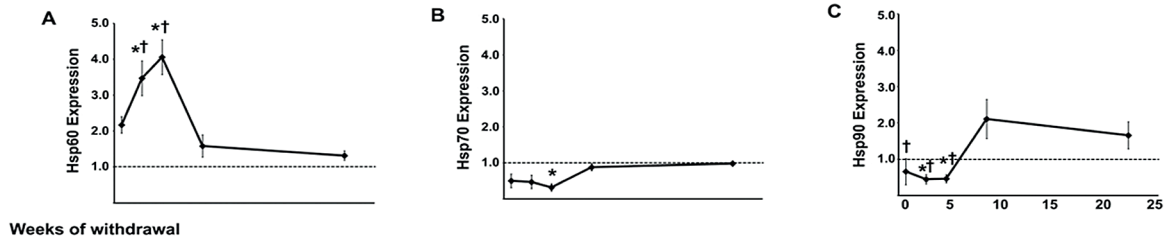

Figure 4: Expression of heat shock proteins (HSPs) in rabbit aortic tissue during atherosclerotic development and stabilisation

*Rabbits were fed a 1 % cholesterol supplemented diet for 8 weeks to induce aortic atherosclerosis. This was followed by up to 22 weeks of a normal diet (cholesterol withdrawal) to stabilise plaque formation. Note: Plaques continued to grow for 8 weeks even during the withdrawal stage before it finally stabilised as a mature plaque and then began to regress without further growth after 8 weeks without supplementation of dietary cholesterol. Western blot analysis is depicted here for HSP60 (A), HSP70 (B) and HSP90 (C) expression after 0, 2, 4, 8 and 22 weeks of withdrawal from cholesterol feeding. Protein expression levels are normalised to total actin and are represented as fold change to control samples. Values are means ± SEM), n = 3-4. *p < 0.05 versus 22 weeks of cholesterol withdrawal; †p < 0.05 vs 8 weeks of cholesterol withdrawal.*

Interestingly, in *in vivo* experiments using cholesterol feeding to rabbits to induce atherosclerosis followed by an extended period of dietary cholesterol withdrawal to slow down the atherogenesis until it stabilised,[72] the only HSP expression that correlated with the atherogenesis (that continued during the initial weeks of cholesterol withdrawal and then dissipated with time) was HSP60 (Figure 4).

These observations were followed with a more focused study of the cytosolic mechanisms whereby HSP60 may initiate cell proliferation. HSP60 overexpression induced vascular smooth muscle cell growth in vitro. The mechanism involved a stimulation of the rate of nuclear protein import.[73] An interaction of Ran protein with HSP60 was particularly key.[73] In addition, an induction in the expression of nuclear import associated proteins and nucleoporins in these cells was also observed.[73] In summary, these findings are consistent with the conclusion that HSP60 promotes cell growth via an action on nuclear transport in the VSMC.[73]

Extracellular mechanisms of HSP60

Under pro-atherosclerotic conditions, damaged vascular cells can secrete HSP60 through exosomal pathways,[57, 74] which acts as an autocrine and paracrine hormone[75, 76] capable of activating vascular cells through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs).[77] For example, chlamydial and human-derived HSP60 can directly activate EC, VSMC and macrophage cellular functions that are important in atherogenesis.[78] Moreover, exposure of cultured VSMC to chlamydial and human HSP60 stimulates cell proliferation through a TLR-dependent mechanism.[56] Thus, vascular cells recognise extracellular HSP60 as a danger signal that promotes inflammation.[75]

Clinical studies demonstrate a strong association between HSP60 levels in the circulation and atherosclerotic vascular disease.[79-82] Initial clinical studies determined that elevated levels of soluble HSP60 were associated with early atherosclerosis.[80, 81] Subsequently, a large case control study showed that increased circulating levels of HSP60 were associated with an increased risk of atherosclerosis.[82]

Autoimmune mechanisms of HSP60

Endothelial cells activated by atherosclerotic risk factors can express biochemically modified HSP60 and cell adhesion molecules on their cell surface.[83] This altered membrane protein expression triggers an autoimmune response whereby T-cells migrate to the activated endothelium and orchestrate production of antibodies and effector T-cells against autologous HSP60. These antibodies and T-cells can have cytotoxic effects on HSP60 expressing vascular cells within lesions.[84-86] Soluble HSP60 can be released from these damaged cells,[62] whereupon it can activate vascular and immune cells to propagate inflammation.

Human and bacterial HSP60 have considerable sequence homology.[87, 88] Consequently humans exposed to microbial HSP60 (eg *chlamydial* HSP60) through infection or vaccinations develop similar cellular and humoral immunity responses as they do when exposed to human HSP60.[62, 88, 89] Thus, protective immunity against microbial HSP60 may promote cross-reactivity with autologous HSP60 when endothelial cells are stressed by atherogenic stimuli.[62, 89]

The concepts and implications of HSP60 autoimmunity and HSP60 cross-reactivity by the humoral immune response are exhibited in a number of clinical and experimental studies. In human atherosclerotic plaques, the expression of *chlamydial* and human HSP60 is associated with HSP65 antibodies.[90] Circulating antibodies against mycobacterial HSP65 can also react with endogenous HSP60 expressed on the surface of endothelial cells in human plaques.[91] Higher titres of HSP65-reactive antibodies were found in individuals with atherosclerosis as compared to individuals without the disease.[92] Furthermore, higher titres of anti-human HSP60 autoantibodies are correlated with advanced stages of atherosclerosis.[93] Consequently, anti-HSP65 antibody titres may be a valuable prognostic marker for atherosclerosis.[92]

In hypercholesterolaemic rabbits, addition of recombinant mycobacterial HSP65 induces endogenous HSP65 expression in the plaque and stimulates production of T-cell populations against HSP65, which drives atherosclerotic development.[94] Indeed, effector T-cells reactive to HSP60

are prominent in the early development of human atherosclerotic lesions.[93] The stimulation of atherosclerosis by the addition of exogenous HSP60 in rabbits and the association of antibodies against HSP60 in more advanced atherosclerosis in humans may appear contradictory at first. However, the antibody response is likely merely a reaction to the abnormally high levels of HSP60 found in the circulation and tissue. Cellular immunity to HSP60 could play a role in the initiation of atherosclerosis, potentially in part through the induction of regulatory T cells, while the humoral response to HSP60 may be responsible for disease propagation.[62]

In addition to its pro-inflammatory effects on T-cells, HSP60 can also have anti-inflammatory effects through the induction and maintenance of regulatory T-cells.[89, 95, 96] Soluble HSP60 can activate regulatory T-cells through TLR mediated signalling pathways.[97] Regulatory T cells are able to modulate HSP60-reactive cytotoxic T-cell activity via anti-inflammatory cytokines and cell-cell contact.[97] This concept has been examined in various atherosclerotic animal models. Oral and nasal immunisation of atherogenic mice with HSP60 and small HSP60-peptides produced a significant reduction in atherosclerotic plaque size through increases in regulatory T-cells.[98, 99] In addition, oral and nasal immunisation with mycobacterial HSP65 protects against atherosclerosis in LDL receptor deficient mice.[100, 101] Lastly, subcutaneous immunisation of ApoE null mice with HSP65 attenuates the development of atherosclerotic lesions.[102] Hence, developing immune tolerance against HSP60 through vaccination with HSP60 and HSP60-derived peptides could be a treatment strategy for atherosclerosis.[62, 89]

Summary

Various atherogenic stimuli (ie oxLDL, mechanical stretch and *Chlamydophila pneumoniae*) can induce HSP60 and stimulate VSMC proliferation.[58, 59, 73, 103] Furthermore, HSP60 has been implicated in the pathogenesis of atherosclerosis.[61] The mechanistic link of HSP60 with stress-induced VSMC proliferation and its pathological sequelae like atherosclerosis may involve a stimulation of the rate of import of proteins into the nucleus of the vascular smooth muscle cell.[73, 103] The imported proteins include nucleoporin and

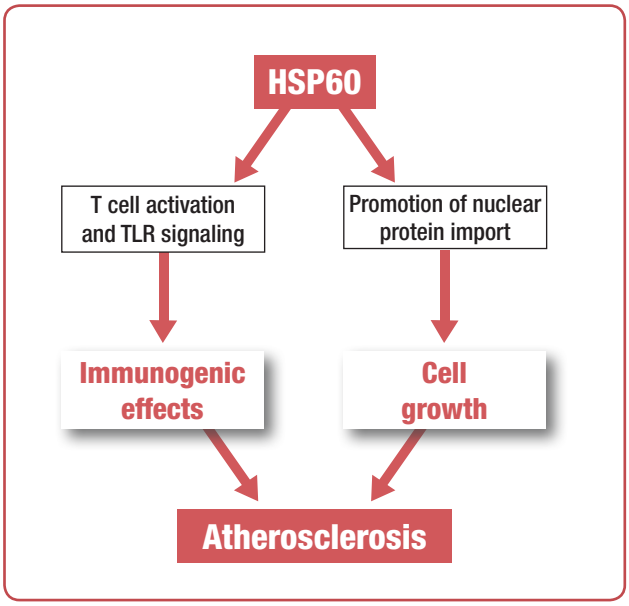

Figure 5: Schema for the involvement of heat shock protein 60 (HSP60) in atherosclerosis

the enhanced expression of a variety of nuclear transport receptors, as well as an augmentation of Ran activity.[73, 103] The existing literature suggests that HSP60 may function as a common downstream regulator of VSMC proliferation during atherosclerotic development. This conclusion is supported by recent data using either specific peptides or a vaccine which targeted HSP60. Both strategies have shown beneficial effects against atherosclerosis.[63, 65, 66, 98, 99] The treatment strategies decreased pro-inflammatory cytokine production,[66] reduced inflammation, modulated the activity of immune cells,[63] reduced fat deposition in the plaque and decreased cholesterol aggregation and plaque thickness.[65] In summary, therefore, the data strongly support an involvement of HSP60 in atherogenesis through both pro-inflammatory and cell proliferative effects (Figure 5). HSP60 remains a promising pharmaceutical target to deter the progression of atherosclerosis.[73]

Conclusion

In conclusion, HSP60 may have an important role to play in vascular diseases like atherosclerosis. HSP60 may be a promising future pharmaceutical target to focus upon in order to deter the pathological effects of disease conditions like hypertension and atherosclerosis.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve human participants or experimental animals. Therefore, the ethics approval was not required in this paper. Some of the data presented in this paper are part of already published studies and those studies and their protocols were approved by the Animal Care Ethics Review Board of the University of Manitoba, Winnipeg, Canada in 2008.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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